

Chronic delta hepatitis: a single-center experience

Chronic delta hepatitis

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Abstract

Aim: Chronic Delta Hepatitis (CDH) is characterized by rapid progressive liver disease. The only treatment option accepted today is pegylated interferon. In this study, we aimed to share the results of the patients who were diagnosed with delta hepatitis and completed the treatment in our hospital, which is the only health care center in Siirt province, which is the eastern province of Siirt, Turkey.

Materials and Methods: Anti HDV antibodies were evaluated in all patients with chronic hepatitis B. All Anti HDV and HDV RNA positive patients were included in this study. The files of these patients were retrospectively reviewed. HDV RNA levels, transaminases, and prothrombin times, abdominal ultrasonographic examinations, and liver biopsies of these patients were recorded. In the patients who started pegylated IFN treatment, transaminases levels and HDV RNA values were recorded at 3, 6, and 12 months. A total of 22 patients were positive for HDV RNA. Four of all patients did not accept the treatment. Due to depression, two patients could not be treated, and one patient could not be treated because of deep thrombocytopenia. The treatment was discontinued due to non-compliance with the treatment in 4 patients.

Results: A total of 11 patients received 48 weeks of pegylated IFN treatment. Four patients had a permanent viral response. One patient was unresponsive to treatment. Relapse was observed in six patients. All alanine transaminase levels of the patients who had viral response decreased to normal range. The most common side effects are weakness, rash, headache, depression.

Discussion: Unfortunately, CDH is not being treated successfully. However, as in our study, a permanent viral response can be obtained in one of three patients and prevented from circulating to these patients. In order to succeed in the treatment of delta hepatitis, further studies are needed and more effective antivirals are needed.

Keywords

Chronic Delta Hepatitis; HDV RNA; Chronic Hepatitis; Interferon

DOI: 10.4328/ACAM.20061 Received: 2019-10-23 Accepted: 2019-10-30 Published Online: 2019-11-01 Printed: 2020-07-01 Ann Clin Anal Med 2020;11(4):307-310

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Introduction

Hepatitis delta virus (HDV) is a defective pathogen that needs hepatitis B virus (HBV) to induce infection. The hepatitis B surface antigen envelope protein protects the HDV nucleocapsid antigen and provides a means for the virus to enter and exit the hepatocyte [1]. Although Chronic Delta Hepatitis (CDH) is rarely seen infection, it has the most severe prognosis due to its consequences. It is believed that about 15 million people are infected with HDV and in 70% of patients with CDH, cirrhosis develops [2].

CDH leads to more severe liver disease than chronic HBV mono-infection with an accelerated course of fibrosis to cirrhosis, early decompensation, and an increased risk of hepatocellular carcinoma (HCC) [3].

Treatment of delta hepatitis is still failed to achieve the desired success. To date, many treatment options have been tried such as nucleoside analogs monotherapy or combined with interferon, Myrcludex B, a synthetic N-acetylated preS1 lipopeptide, Irbesartan, Ezetimibe, and ritonavir and Cyclosporin A, Lonafarnib (Lonafarnib, a prenylation inhibitor significantly reduces virus levels in hepatitis delta patients) but the only treatment that is still considered effective is interferon alpha [1].

In this study, we aimed to present findings of our chronic hepatitis patients infected with HDV, who were treated with pegylated subcutaneous interferon (IFN) per week for 48 weeks duration.

Material and Methods

Anti-HDV antibodies were evaluated in all patients with chronic hepatitis B. All anti-HDV and HDV RNA positive patients who admitted to our outpatient clinics between October 2013 and September 2015 were enrolled in this study. Files of these patients were retrospectively reviewed. A total of 22 patients, 14 males and 8 females with hepatitis B surface antigen (HBsAg) (+), AntiHbc IgM (-), antibody against hepatitis D virus (anti HDV) and/or HDV RNA (+), who had no contraindications for treatment and had suitable histological activity index (HAI) and fibrosis scores in their liver biopsies were enrolled. HBsAg, hepatitis B e antigen (HBeAg), HDV RNA levels, transaminases and prothrombin times, abdominal ultrasonographic examinations and liver biopsies of these patients were recorded. Transaminases and HDV RNA values at 3, 6, 12 months in the patients who started pegylated IFN treatment were recorded.

Exclusion criteria: Seropositivity for hepatitis C virus, Human immunodeficiency virus, any other chronic liver disease, serious comorbid disease, decompensated liver disease, HCC, leukopenia (<3000/mm³), thrombocytopenia (<50000/mm³), A total of 22 patients were positive for HDV RNA. Four of all patients did not accept the treatment. Due to depression, two patients could not be treated, and because of deep thrombocytopenia one patient could not be treated. Treatment was discontinued due to severe side effects in 4 patients.

All examinations were carried in biochemistry, hematology, pathology and microbiology laboratories of our hospital. Staging of HAI and fibrosis was performed according to Knodell scoring. The biochemical response was defined under two-fold upper limit of serum alanine transaminase (ALT) level at the end of the treatment, a virological response as the absence of serum HDV RNA at the end of the treatment and completed or sus-

tained virological response (SVR) as a negative qualitative PCR, 6 months after the treatment cessation. Patients remaining HDV RNA positive at the end of the treatment were considered to be "non-responders". Patients who were HDV RNA-negative at the end of the treatment and became positive 6 months after treatment cessation were considered as relapse.

Results

The baseline characteristics of the patients who completed the 48-week IFN treatment are shown in Table 1; pretreatment and follow up to 18 months HDV RNA and ALT values are given in Table 2. Initially, serum HBsAg was positive in all patients while HBV DNA was positive in 11 patients. HBeAg was positive in only two patients.

A total of 22 patients were included in the study eleven of them received 48 weeks of pegylated IFN treatment. Four patients had a permanent viral response that their HDV RNA levels were equal to zero and biochemical response that their ALT levels decreased to normal range. One patient was unresponsive to treatment. Relapse on the sixth month after the end of treatment was observed in six patients. All ALT levels of the patients who had viral response decreased to normal range (Table 2,3). At the end of the treatment, serum HBV DNA was negative in all patients but six months later, increased to a measurable level in two of them.

In none of the patients HBsAg negativity was observed.

At the end of the treatment, serum HDV RNA was negative in all patients but seven of them were positive at eighteenth months. Transaminase levels of five patients were 2-times upper limit of normal values at initially, transaminase level of four patients was increased during the treatment, apart from one patient who was unresponsive to the treatment, in all others, transaminase levels were lower than two times upper limit of its, at the end of the treatment. These values remained the same in the sixth month after cessation of the treatment.

Table 1. Baseline characteristics of all patients

Patient's no	S/A	HBV DNA	HbeAg	Fibrosis	Treatment
1.	F/18	+	-	2	C
2.	F/56	+	-	3	C
3.	M/27	+	-	2	C
4.	M/25	+	+	2	C
5.	M/29	+	-	1	C
6.	M/47	+	-	2	C
7.	M/53	+	-	3	C
8.	F/36	-	-	1	C
9.	M/47	-	-	3	C
10.	M/67	+	+	2	C
11.	F/37	+	-	1	C
12.	M/28	+	-	2	I
13.	M/53	-	-	2	I
14.	F/47	-	-	3	I
15.	M/39	+	-	3	I

F: female| M: male; S: sex; A: Age; C: completed; I: incompleated

The most common side effects are weakness, rash, headache, depression but none of these were the side effects that would cause the cessation of the treatment. All patients had completed the treatment.

Discussion

Although CDH is the less frequently encountered, it is the most severe form of viral hepatitis affecting humans. Hepatitis D virus, discovered in 1977, in Italy by Rizzetto is a defective virus, requires hepatitis B surface antigen (HBsAg) for transmission. Hepatitis delta occurs either as acute or chronic infection. CDH is a serious form of chronic liver disease with an accelerated course leading to early cirrhosis, decompensation, and hepatocellular carcinoma [4]. Worldwide, there are approximately 240 million individuals chronically infected with the hepatitis B virus (HBV), including 15-20 million coinfecting with the hepatitis D virus [5].

No evidence-based rules for treating CDH exist and treatment duration needs to be individualized based on virologic response at end of treatment or end of follow-up. Effective treatment may decrease liver-related complications, such as decompensation or liver-related mortality. In patients with decompensated cirrhosis, interferons are contraindicated and liver transplantation has to be considered. Alternative treatment options are an urgent need in CDH. New treatment strategies targeting different steps of the HDV life cycle such as hepatocyte entry inhibitors or prenylation inhibitors are emerging and provide hope for the future. Although delta hepatitis continues to be a major medical scourge worldwide and many studies have been evaluated on its treatment, the only approved treatment agent for HDV is interferon (IFN)-α pegylated interferon. However, the currently accepted and appropriate treatment method is the weekly peg IFN treatment for 48 weeks even if the desired success has not been achieved yet [6,7].

Table 2. Levels of serum HBV DNA and serum HDV RNA during the study

Patient's no	HBV DNA	HDV RNA (IU/mL)	HDV RNA (IU/mL)	HBV DNA	HDV RNA (IU/mL)	HDV RNA (IU/mL)
1.	+	1780000	246	-	0	0
2.	+	144000	120000	-	0	376000
3.	+	276000	0	-	0	34800
4.	+	2860000	6350	-	0	196000
5.	+	579000	0	-	0	0
6.	+	7500000	1200	-	0	3244000
7.	+	1500000	1200	-	89000	-
8.	+	343000	0	-	0	24000
9.	+	2900000	376	-	0	0
10.	+	140000	0	-	0	468000
11.	+	837000	0	-	0	28000

Since CDH is dependent on HBV, the war against HBV is also important in preventing this infection. HBV vaccination, the improvement of sanitation and living conditions, and sexual restraints prompted by the risk of AIDS can lead to the containment of HBV with a significant reduction of HBsAg carriers and finally can reduce the HDV transmission.

In this study, although, at the end of the treatment, serum HDV RNA was negative in all patients, seven of them were positive at posttreatment week-24. The posttreatment week-24 virologic response is the most widely used surrogate marker of treatment efficacy, but it does not represent a sustained virologic response, and late relapse can occur. As an easy-to-use simple serological test, anti-HDV- immunoglobulin M (IgM) correlates with histological inflammatory activity and clinical long-term outcome; however, it is not as sensitive as HDV RNA in assessing treatment response.

IFN can decrease aminotransferase levels, improve liver histology and protect from progress to cirrhosis. In this study, apart from one patient who was unresponsive to the treatment, serum transaminase levels of all others were lower than its two times upper limit at the end of the treatment. However, she had not virologic remission at the end of the treatment, her serum transaminase values decreased compared to the pretreatment values. These values remained the same in the sixth month after cessation of the treatment. Serum transaminase values of four patients increased at the twelfth week of treatment, one of them was unresponsive to treatment. Serum transaminase levels of all others in the sixth month of the end of the treatment were lower than twice the upper normal level. These results showed that the virological response and biochemical response were correlated. A review of the literature on the subject showed that in several studies IFN α had an impact on normalization of ALT value during therapy but this effect did not last during the follow-up course, at all times [8,9].

Table 3. Levels of ALT during the study

Patient's no	ALT (IU/mL) initial	ALT (IU/mL) 12 weeks	ALT (IU/mL) 24 weeks	ALT (IU/mL) 48 weeks	ALT (IU/mL) 18 months
1.	102	140	110	40	30
2.	45	44	36	59	35
3.	140	128	96	48	34
4.	113	132	86	40	62
5.	56	40	32	28	30
6.	37	42	31	24	56
7.	178	246	156	96	58
8.	49	57	38	27	35
9.	84	48	94	42	22
10.	22	20	19	24	28
11.	19	20	34	46	58

F: female M: male; S: sex; A: Age; C: completed; I: incomplected

It is known that the dominant virus is delta in CDH and suppresses HBV DNA replication and therefore HBeAg and HBV DNA are often negative. In this study, the results were different from the literature, and the majority of our patients were still serum HBeAg positive. It is known that the negativity of serum HBV DNA with or without treatment in delta infection does not mean complete response. However, HBsAg loss can provide this, unfortunately, this is not so common, and in the literature, HBsAg seroconversion has been demonstrated in a small number of patients. Lau et al. [10] observed HBsAg seroconversion in 4 of 6 patients, Battagay et al. [11] also observed this seroconversion in 3 of 17 patients, Ormeci et al. [12] observed HBsAg seroconversion in 2 of 12 patients with delta hepatitis. In this study, unfortunately, any HbsAg seroconversion was observed in our patients.

The main aim of the treatments is HDV RNA negativity and its persistence during the follow-up period. At the sixth month of the treatment, only one patient had positive result for HDV RNA levels. Unfortunately, we had no serum HDV RNA levels of patients and control liver biopsies after 1 or 2 years after the end of the treatment. These might be considered as limitations of the study but decrease to normal levels or normalization in serum transaminase and loss of HDVRNA levels were considered as response to the treatment. We did not perform control liver biopsies because control biopsy is not recommended by the guideline for managing delta hepatitis. In addition, control liver biopsy is not cost-effective since it does not impose an additional benefit. As mentioned before, although the results of the first year or second year after the end of the treatment were not known, continued negativity of serum HDV RNA levels at the sixth month after the end of the treatment shows the success of the treatment. Among participants in Keshavari et al.'s study, 12 (60%) patients lost HDV RNA at the end of treatment but this situation was stable for only 3 (15%) subjects at the end of the follow-up period. In a study by Niro et al., the rate of final response (SVR) was similar (12%) to that determined in the present study [13]. Also, Abbas et al. reported SVR in about 17% of IFN α treated patients [14,15]. Our results can be evaluated as similar or high success compared to the literature.

Delta hepatitis is known to cause a rapid progressive liver disease. In this study, five of fifteen patients had stage ≥ 3 liver fibrosis. When compared to previous studies, our patients had a lower fibrosis degree. In a study by Keshavari et al., 40% of patients had stage > 4 liver fibrosis [14]. In other studies by Niro et al. and Farci et al., almost half of the patients had cirrhosis according to liver biopsies [6,16]. One of the important factors in response to treatment is thought to be the histological stage of the liver. This may be a reason for the high virological response in our study.

Conclusion

CDH is still a serious health problem due to a lack of effective treatment. Besides all these, IFN is the only effective treatment option in CDH and it can decrease aminotransferase levels to normal levels, improve liver histology and protect from progress to cirrhosis. More effective therapeutic modalities are needed in CDH.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Ayşe Kefeli. Chronic Delta Hepatitis: A single-center experience. *Ann Clin Anal Med* 2020;11(4):307-310